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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,990	01/04/2005	Nicoletta Bianchi	Q85654	3209

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,990	BIANCHI ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/13/06, 1/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of species rapamycin, and hydroxy urea in the reply filed on 12/22/06 is acknowledged. The traversal is on the ground(s) that the use claims have been converted to method claims and applicants argue that methods of using compounds of rapamycin or structural analogs thereof are non-obvious and novel and the method of treating beta-thalassaemia using effective amounts of rapamycin or structural analogs thereof is a contribution over prior art. This is not found persuasive because the rapamycin or structural analogs thereof are structurally distinct chemical compounds and the inventions restricted are patentably distinct. The search for each of the inventions is not co-extensive particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement, and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes as indicated above is deemed proper.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Johnston, et al., Blood, 98, 410.

In the instant application, applicants claim a method of treating β-thalassaemia comprising administering a medicament comprising a pharmaceutically effective amount of rapamycin or a structural analog thereof to a patient in need of such treatment.

Johnston, et al., teaches a method of treatment for β-thalassaemia in a heterozygous murine model that carried deletions for both b1 (beta major) and b2 (beta minor) adult globin chains for thalassaemia. In the absence of a regulated expression the mouse model injected with AAV vectors expressing murine erythropoietin (epo) led to very high levels of serum epo and ultimate death of all model animals. However, the subsequent induction with rapamycin of AAV vectors expressing inducible epo led to a dose dependent increase in epo. It was also found that no detectable expression of epo in the absence of rapamycin and the induction was reversible. Thus the anemia associated with induced β-thalassaemia in this mouse model was treated with gene therapy wherein the gene expression was controlled by rapamycin. Therefore, the claim 1 is anticipated by the cited reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston, et al., Blood, 2001, 98, 410 in view of Rachmilewitz, British Journal of Haematology, 1995, 91, 263-268.

In the instant application, applicants claim a method of treating β-thalassaemia comprising administering a medicament comprising a pharmaceutically effective amount of rapamycin or a structural analog thereof to a patient in need of such treatment. The method wherein the rapamycin or the structural analog is in combination with at least one modifier of a transcription process selected from the group consisting of cytosine arabinoside, retinoic acid, plicamycin, mithramycin, hydroxyurea, guanine, guanosine, triphosphate (GTP), gaunosine diphosphate (GDP) and guanosine monophosphate (GMP).

The reference of Johnston teaches a method of treatment for β-thalassaemia in a heterozygous murine model that carried deletions for both b1 (beta major) and b2 (beta minor) adult globin chains for thalassaemia. In the absence of a regulated expression, the mouse model injected with AAV vectors expressing murine erythropoietin (epo) led to a very high levels of serum epo and ultimately caused the death of all model animals. However, the subsequent induction with rapamycin of AAV vectors expressing inducible epo led to a dose dependent increase in epo. It was also found that no detectable expression of epo in the absence of rapamycin and the induction was reversible. Thus the anemia associated with induced β-thalassaemia in this mouse model was treated with gene therapy wherein the gene expression was controlled by rapamycin. The treatment method of Johnston, et al., does not teach the combination with a modifier of a transcription process such as hydroxyurea.

Rachmilewitz teaches novel treatments for β-thalassaemia, which is a severe β-globin gene disorder. The β-thalassaemia disorders result in individuals who are homozygous for mutations (or deletions) in or around β-globin chain clusters (page 1, column 1, paragraph 1). The reference discloses that several agents are being studied for their ability to augment the post-natal synthesis of fetal haemoglobin (HbF) in patients with sickle cell and β-thalassaemia (page 263, column 2, paragraph 3) and hydroxyurea (HU) is the least toxic of several chemotherapeutic agents (page 264, column 1, paragraph 2). The HU reagent has been reported to be efficacious in patients with sickle-β-thalassaemia (page 265, column 1, paragraph 1). The reference also teaches that therapies based on the modulation of existing gene expression, given alone or in combination with other therapies, appear to offer significant promise in favorably modifying the clinical course of patients with sickle-cell disease and β-thalassaemia (page 266, column 2,

paragraph 2). The reference further discloses that rHuEpo have been shown to augment HbF levels in erythroid cell culture and in experimental animals. On this basis rHuEpO has been used in clinical trials and found to increase the percentage of F reticulocytes and HbF in sickle-cell patients when administered in high doses along with iron supplementation. Moreover, it seems that rHuEPO exerts an additive effect when given with HU in alternating doses. This is indicative of the fact that HU has been effective in a combination therapy with other agents in increasing the HbF levels in animal models (page 265, column 1, paragraph 2).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Johnston and Rachmilewitz to develop a treatment method for β-thalassaemia by administering a medicament comprising a pharmaceutically effective amount of rapamycin and hydroxyurea, because, Johnston teaches the method of administering rapamycin to treat β-thalassaemia in murine models and Rachmilewitz teaches administration of hydroxyurea to treat β-thalassaemia. Rachmilewitz further teaches that rHuEpO has been used in clinical trials and it has been found to increase the percentage of F reticulocytes and HbF in sickle-cell patients when administered in high doses along with iron supplementation. According Rachmilewitz, it appears that rHuEPO exerts an additive effect when given with HU in alternating doses. According to MPEP. 2144.06, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious". The motivation to do

so comes from the fact that such studies have been reported in the cited reference of Rachmilewitz wherein a controlled trial of recombinant human EPO (rHuEpo) and HU have shown improvement in the quality and quantity of the newly formed red blood cells (RBC) compared to the use of each of the reagents alone (page 265, column 1, paragraph 3). The reference also states that therapies based on the modulation of existing gene expression, given alone or in combination with other therapies, appear to offer significant promise in favorably modifying the clinical course of patients with sickle-cell disease and β-thalassaemia (page 266, column 2, paragraph 2). There would have been reasonable expectation of success in a combination therapy given the fact such a therapy has been successfully been carried out as disclosed by Rachmilewitz as stated in earlier.

Therefore, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time of invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3 and 4 recites the limitation "modifier of transcription process" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654

2/1/09
ANISH GUPTA
PRIMARY EXAMINER